REMARKS

Status of the Claims

Claims 1, 3 and 7 are pending. Claims 1, 3 and 7 are rejected. Claim 1 is amended herein. Claims 2, 4-6 and 8-22 were canceled previously and claim 3 is canceled herein. No new matter has been added.

Amendments

Applicants have revised the claim amendments to recite the elected species bismuth-213, as discussed *infra*, and to correct the response to the rejections in the Final Office Action, mailed May 2, 2005. This Response after Final, initially filed October 12, 2005, was the submission provided with the Request for Continued Examination, filed October 31, 2005.

Claim amendments

The preamble of claim 1 is amended to recite a method of sequentially reducing the size of a solid tumor until tumor growth cannot recur (pg. 11, ll. 5-8). Claim 1 is amended to limit the alpha emitting isotope used in the antibody construct to bismuth-213, as recited in dependent claim 3, and to limit the high specific activity to a range of about 10 mCi/mg to about 30 mCi/mg (pg. 11, ll. 14-15; pg. 12, ll. 9-16). The range of high specific activities recited previously in the claim 1, i.e., 0.1 mCi/mg to about 30 mCi/mg, encompasses all suitable alpha emittors, such as those recited in claim 3. For example, actinium-225 falls within

the lower end of the range and bismuth-213 falls within the higher end of the range. Claim 3 is canceled.

Claim 1 also is amended so that the characterizing clause in original step (c) is a specific method step of selecting a dose of the construct to provide a pharmacologically effective amount of antibody to bind to a sufficient plurality of the targeted sites on each tumor cell (pg. 17, ll. 8-11) on an outer layer of tumor cells comprising the solid tumor so that a minimum of two atoms of bismuth-213 delivers an alpha track to at least one tumor cell (pg. 48, ll. 13-21) comprising at least said outer layer upon binding the antibody thereto (pg. 39, ll. 7-9; pg. 48, ll. 3-9). Furthermore, claim 1 is amended to clarify that repeated administration kills at least one additional layer of tumor cells thereby sequentially reducing the size of the solid tumor until tumor growth cannot recur (pg. 39, ll. 5-9; pg. 48, ll. 7-11). No new matter was added in this amendment.

The 35 U.S.C. §103(a) rejection

Claims 1,3 and 7 are rejected under 35 U.S.C. §103(a) as being unpatentable over **Simonson** *et al.* (Cancer Res., 50(3 Supp): 9855-9885 (1990)), of record, in view of **Kaspersen** *et al.* (*Nuclear Med Comm*, 16, pp. 468-476 (1995)), of record, **Lemelson** (U.S. Patent No. 4,665,897) and **Blankenberg** *et al.* (U.S. Patent No. 6,197,278) or **Vieria** (Eur J Surgical Oncology, 22(4): 331-334 (1996)) and further in view of **Goldenberg** (U.S. Patent No. 4,444,744). Applicant respectfully traverses this rejection.

The Examiner maintains the reasons for rejection already of record in the paper of 10/21/2004. The Examiner states that the specification does not disclose a definition of "killing a solid tumor" or that using the claimed labeled antibody would achieve a cure of 5 year disease-free survival or that using the claimed labeled antibody would achieve a cure of 5 years disease-free survival. The Examiner also states that a cure of at least 5 years disease-free survival is not recited in the claims nor is it a result found in any of the cited examples in the specification. Thus, the Examiner contends that "killing a solid tumor" as recited in claims 1, 3 and 7 encompasses treating a tumor, i.e, some tumor cells are killed, which is certainly taught by **Simonson** *et al.*

Applicants have amended claim 1 to recite a method of sequentially reducing the size of a solid tumor greater than 1 mm in size until tumor growth cannot recur (pg. 11, ll. 5-8; pg. 39, ll. 5-9). Applicants also have amended claim 1 to recite bismuth-213, recited in dependent claim 3, as the alpha-emitting isotope comprising the high-specificity antibody construct. The specification teaches that using the selected high specific activity alpha-emitting antibody constructs it is possible to first selectively kill the first outer layers of a tumor and thereby expose the next inner layers for killing. Repeated doses of construct, separated in time to allow the death of the outer layers, sequentially kills layers of cells until a core which does not grow further is reached which is itself finally removed with another dose of construct (pg. 48, ll. 3-9). The specification states this makes it possible to kill larger tumors.

Particularly, the specification demonstrated that a single dose of bismuth-213 has eliminated 5 to 6 layers of cells in a spheroid model, leaving behind a previously unexposed "core" of cells that can then be targeted by a subsequent administration (pg. 11, ll. 3-8; pg. 39, ll. 5-9; Fig. 2). Although Applicants have amended the preamble and claim steps, as discussed, the specification certainly defines killing a solid tumor as repeatedly or sequentially killing tumor cells in exposed outer layers of the solid tumor until the non-growing core itself is gone. Such claim elements are not taught or suggested by **Simonson** *et al.*

As discussed *supra*, Applicants have amended claim 1 to recite a range of specific activities for bismuth-213 labeled antibody of about 10 to about 30 mCi/mg from which a specific activity is selected so that a selected dose of antibody construct will deliver sufficient alphas per tumor cell to kill at least a layer of cells comprising the solid tumor upon each intravenous administration thereto until tumor growth cannot recur. **Simonson** *et al.*, as primary reference, fairly teach that bismuth-212 constructs may be appropriate to treat large peritoneal tumors when administered interperitoneally, but that its short half-life limits its use in vivo (pg. 987s, 1st col. 1st PP). **Simonson** *et al.* neither teach nor suggest that bismuth-213 would be appropriate to treat any type of solid tumors via intravenous injection of a bismuth-213 construct with Applicants' claimed high specific activity.

Simonson *et al.* do not teach or suggest specifically designing high specific activity antibody constructs as in Applicants' invention. **Simonson** *et al.* are silent as to the actual specific activity of the bismuth-212/antibody construct

used in any administered dose. In fact, **Simonson** *et al.* simply disclose that the specific activity of the bismuth-212/antibody construct ranged from 5-10 μCi/μg (pg. 985s, 2nd col., 9th PP). Even should one of ordinary skill in the art assume it was 10 mCi/mg, which is the upper limit of the 5-10 μCi/μg and even though **Simonson** *et al.* found no observable tumor upon dissection after multiple i.p. injections of 180 μCi, the reference states that no cures were obtained for the tumor bearing mice (pg. 987s, 2nd col., 1st PP).

Therefore, one of ordinary skill in the art cannot conclude that a recurrence in growth is prevented even without observable tumor after treatment with bismuth-212. Applicants teach that the limit of detectability of a solid tumor is 1 gram or 10^9 cells. To achieve a "cure", defined as 5-year disease free survival, the probability that all tumor cells are killed must approach one. To achieve this, Applicants teach that a minimum high specific activity of the antibody construct is, *inter alia*, an integral characteristic of its description. Applicants teach that to reduce tumor size to a point where tumor growth does not recur using alpha emittors requires designing an alpha emitting radiolabeled antibody construct which must take into consideration at least the high specific activity, dependent upon the alpha emittor used, the half-life of the alpha emittor, the type of antibody, the number of target sites, etc., to be able to select a suitable dose of the designed labeled antibody to effectively kill the solid tumor. Without considering these features, it is not possible for someone skilled in the art to prepare a useful dose.

Kaspersen *et al.* do not remedy these deficiencies. **Kaspersen** *et al.* teach that bismuth-213 may be substituted for Bi-212 for the treatment of single

cell blood borne malignancies, but for the treatment of solid tumors suggests only that actinium-225 may have a possible application in the treatment of metastatic solid tumors (pg. 474, 2nd col.). In establishing obviousness, a combination of prior art must fairly teach or suggest all the claim elements. *Arguendo*, in considering the combination of **Simonson** *et al.* with **Kaspersen** *et al.* one of ordinary skill in the art, might be motivated to peritoneally inject a bismuth-213 labeled antibody as a substitute for bismuth-212 to treat peritonitoneal tumors. The combination of **Simonson** *et al.* with **Kaspersen** *et al.* provides no motivation, not found in Applicants' specification, to specifically design a bismuth-213/antibody with a high specific activity between 10 mCi/mg and 30 mCi/mg in a dose of antibody specifically selected, as described in Applicants' specification, to provide sufficient alphas to kill sequential layers of tumor cells via repeated intravenous administration of the construct to prevent recurrent growth of the solid tumor.

Furthermore, combining **Simonson** *et al.* and **Kaspersen** *et al.* with **Lemelson** and **Blankenberg** *et al.* or **Vieria** and **Goldenberg** does not remedy these deficiencies. The Examiner states that **Lemelson** teaches repeated administration of alpha particles to treat a tumor. Applicants strongly reiterate that **Lemelson** teaches treating a tumor by administering **non-radioactive or inactive nuclide/antibody constructs** (Applicants' emphasis), e.g., boron-10, and activating it by high levels of external beam neutron radiation to cause the inactive nuclide to emit a radioactive particle, e.g., alpha, beta or gamma. The inactive nuclide/antibody is administered again, activated and the monitoring process repeated until treatment ceases (Abstract; col. 12, lines 1-69; col. 13, lines 1-28).

Applicants respectfully maintain that the Examiner must consider all these steps when applying the reference in combination with **Simonson** *et al.* and **Kaspersen** *et al.* to demonstrate obviousness.

As amended, claim 1 specifically recites repeatedly intravenously administering a high specific radioactive bismuth-213/antibody construct. The repeated delivery of alphas sequentially kills tumor cells in exposed outer layers of the solid tumor without any further manipulation. **Lemelson** specifically discloses a method using a non-radioactive antibody composition to target the tumor and then bombards it with neutron radiation to induce alpha emission. At best **Lemelson** suggests that to solve the problem of delivering alpha particles to a tumor is to deliver them in the form of a non-radioactive nuclide, capable of neutron capture to cause alpha emission, which can be targeted to the tumor without the problems associated with radioactive alpha emittors. Nor does **Lemelson** teach a bifunctional chelator to chelate the nonradioactive nuclide to the antibody (col. 5, ll. 20 to col 7., ll. 29).

Lemelson does not fairly teach or suggest that a tumor can be treated by the repeated administration of a radioactive nuclide, such as bismuth-213, with a particularly selected or designed specific activity, as in the instant invention, and thereby forego neutron beam activation of boron-10. Lemelson teaches the administration of a cold boron-labeled antibody which requires an external beam to deliver a radioactive particle which is not predictive of the specific activity of bismuth-213 used in the instant invention. The specific activity of the

boron is not comparable with the specific activity of the bismuth-213. **Lemelson** teaches away from the instant invention.

In fact **Lemelson** *et al.* does not enable the method of tumor treatment using boron-10. **Lemelson** *et al.* only provides enablement for the boron10/antibody construct, but does not even demonstrate *in vitro* that the construct targets and delivers the boron-10 to the targeted cells. At the time of filing the instant invention it was known in the art that in a human boron capture could not be used systemically because it was not possible to generate enough boron at a site locally by intravenous administration to allow enough neutron capture to provide for alpha particle emission.

Nor does adding **Vieira** *et al.* or **Blankenberg** *et al.* and **Goldenberg** to the combination remedy the deficiencies in the combination of **Simonson** *et al.*, **Kaspersen** *et al.* and **Lemelson**. The Examiner states that Viera *et al.* and Blankenberg teach that radiolabeled antibody or annexin reach target cancer cells within minutes after i.v. administration. The Examiner also states that **Goldenberg** teaches the use of radiolabeled antibodies to cancer cell surface antigens for cancer immunotherapy. That some radionuclides can be linked to antibodies for tumor therapy is known as is that intravenously administered radiolabeled antibodies can target specific cells fairly quickly depending on the construct and target cell.

Blankenberg *et al.* teach a method of imaging regions of cell death using technitium-99m linked to annexin by a hydrazine nicotinamide linker (col. 8, ll. 52-54col. 9, ll. 25-28). **Vieira** *et al.* only state that radiolabeled monoclonal

antibodies are an example of a potential imaging agent already under investigation as a means of detecting breast cancer. In the Abstract **Vieira** *et al.* specifically investigate 99mTc-labeled tetrofosmin, that is 99mTc-ethoxy-ethyl phosphinoethane, which is a lipophilic, cationic chemical compound and not a radiolabeled monoclonal antibody. **Goldenberg** teaches that antibodies may be labeled by any technique known in the art (col. 6, ll. 67-68). None of **Vieira** *et al.*, **Blankenberg** *et al.* nor **Goldenberg** remedy the deficiencies in the combination of **Simonson** *et al.*, **Kaspersen** *et al.* and Lemelson of designing bismuth-213/antibody constructs at Applicants' claimed specific activities.

Applicants submit that the combination of **Simonson** *et al.*, with **Kaspersen** *et al.*, **Lemelson**, **Blackenberg** *et al.* or **Vieira** *et al.*, and **Goldenberg** does not render amended claim 1 *prima facie* obvious. At a minimum, no suggestion or teaching is fount to guide one of ordinary skill in the art in the design of a high specific activity bismuth-213antibody construct from the claimed range and to select a dose of the bismuth-213/antibody construct sufficient to bind a plurality of target sites so that at least two bismuth atoms on the tumor cell deliver at least one alpha particle to at least one tumor cell comprising an outer layer of tumor cells. Thus, no motivation is present for one of ordinary skill in the art that does not lead to simply trying. Furthermore, dependent claim 7 depends from amended claim 1 and limits the dose of the antibody. As the combination of **Simonson** *et al.*, with **Kaspersen** *et al.*, **Lemelson**, **Blackenberg** *et al.* or **Vieira** *et al.*, and **Goldenberg** does not render amended claim 1 obvious, then neither can dependent claim 7 be rendered obvious by the combination. Accordingly, in

view of the claim amendment and arguments presented herein, Applicants respectfully request that the rejection of claims 1 and 7 under 35 U.S.C. §103(a) be withdrawn.

Applicants submit that claims 1 and 7, as presented herein, are in condition for allowance. Accordingly, Applicants request that claims 1 and 7 be passed to issuance. This is intended to complete the response to the Final Office Action, mailed May 2, 2005, that was the submission for the Requenst for Continued Examination, filed October 31, 2005. If any issues remain, the Examiner is respectfully requested to telephone the undersigned attorney for immediate resolution. Applicants believe no fees are due. Should this be in error, please debit any applicable fees from Deposit Account No. 07-1185 on which the undersigned is allowed to draw.

Respectfully submitted,

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